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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/770,418	LE MOUELLIC ET AL.	
	Examiner	Art Unit	
	WU-CHENG Winston SHEN	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 May 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *71-77* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *71-77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 February 2009* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *05/12/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments filed 05/12/2009 have been fully considered but they are not persuasive. Claims 71, 76 and 77 are amended. The amendment has been entered. Claims 71-77 are pending and currently under examination.

This application 10/770,418 filed on Feb. 04, 2004 is a CON of 10/639,754 08/13/2003 which is a CON of 08/466,699 06/06/1995 PAT 6,638,768, which is a CON of 08/301,037 09/06/1994 PAT 6,528,313, which is a CON of 08/048,056 04/19/1993 ABN, which is a CON of 07/598,679 12/19/1990 ABN. Relevant foreign applications are FRANCE PCT/FR90/00185 03/19/1990 and FRANCE 89 03630 filed on 03/20/1989.

Claim Rejection - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

1. Previous rejection of claims 71-77 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is ***withdrawn*** because the claims have been amended.

Claims 71, 76, and 77 have been amended and no longer recite the limitation "wherein, the first and second recombination DNA sequences direct homologous recombination events between the first and second endogenous DNA sequences in the genome of the mammalian cell upon introduction of the DNA construct into the mammalian cell, such that the

first and second insertion DNA sequences are inserted into the genome of the mammalian cell between the first and second endogenous DNA sequences". Claims 72-75 depend from claim 71.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Previous new matter rejection of claims 71-77 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, is ***withdrawn*** because the claims have been amended.

Claims 71, 76, and 77 have been amended and no longer recite the limitation "wherein, the first and second recombination DNA sequences direct homologous recombination events between the first and second endogenous DNA sequences in the genome of the mammalian cell upon introduction of the DNA construct into the mammalian cell, such that the first and second insertion DNA sequences are inserted into the genome of the mammalian cell between the first and second endogenous DNA sequences". Claims 72-75 depend from claim 71.

3. Previous scope of enablement rejection of claims 71-77 under 35 U.S.C. 112, first paragraph, is ***withdrawn*** because the claims have been amended.

This withdrawn rejection stated that the specification, while being enabling for a DNA construct for homologous recombination, comprising: (A) a first flanking DNA sequence and a second flanking DNA sequence, wherein the first flanking DNA sequence is homologous to a first endogenous DNA sequence in the genome of a mammalian cell, and the second flanking DNA sequence is homologous to a second endogenous DNA sequence in the genome of the mammalian cell; and (B) a first insertion DNA sequence and a second insertion DNA sequence, wherein the first insertion DNA sequence encodes a first gene product that does not confer resistance to a selection agent involved in the selection of transformants, the second insertion DNA sequence encodes a second gene product that confers resistance to a selection agent involved in the selection of transformants, the second insertion DNA sequence is downstream of the first insertion DNA sequence, the second insertion DNA sequence is operatively linked to regulatory elements that direct expression in transformed cells of the second gene product that confers resistance to the selection agent, and the first gene product is part or all of a receptor; wherein the first and second insertion DNA sequences are located between the first and second flanking DNA sequences in the DNA construct; and wherein upon introduction of the DNA construct into the mammalian cell, *the first flanking DNA sequences recombine with the homologous sequences of the first endogenous DNA sequences in the genome of the mammalian cell, and the second flanking DNA sequences recombine with the homologous sequences of the second endogenous DNA sequences in the genome of the mammalian cell*, such that the first and second insertion DNA sequences are inserted into the genome of the mammalian cell between the first and second endogenous DNA sequences, **does not** reasonably provide enablement for said DNA construct wherein *the first and second recombination DNA sequences direct*

homologous recombination events between the first and second endogenous DNA sequences in the genome of the mammalian cell upon introduction of the DNA construct into the mammalian cell.

Claims 71, 76, and 77 file don 05/12/2009 have been amended and no longer recite the limitation "wherein, the first and second recombination DNA sequences direct homologous recombination events between the first and second endogenous DNA sequences in the genome of the mammalian cell upon introduction of the DNA construct into the mammalian cell, such that the first and second insertion DNA sequences are inserted into the genome of the mammalian cell between the first and second endogenous DNA sequences". Claims 72-75 depend from claim 71.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

4. Previous rejection of claims 71 and 73 under 35 U.S.C. 103(a) as being unpatentable over **Mansour et al.** (Mansour et al., Introduction of a lacZ reporter gene into the mouse int-2 locus by homologous recombination. *Proc Natl Acad Sci U S A.* 87(19):7688-92, 1990) in view of **Petkovich et al.** (Petkovich et al. A human retinoic acid receptor which belongs to the family of nuclear receptors. *Nature* 330(6147): 444-50, 1987), is ***withdrawn*** because Applicant's arguments file don 05/12/2009 have been fully considered and found persuasive.

Applicant argues that the priority date of this application is March 20, 1989 (the filing date of FRANCE 89 03630), and the United States filing date is March 19, 1990 (the filing date of PCT/FR90/00185), as no new matter is introduced. Applicant states that Mansour et al. was published after both of those dates; in October of 1990 (See pages 11-12 of Applicant's remarks file don 05/12/2009).

5. Previous rejection of claim 76 under 35 U.S.C. 103(a) as being unpatentable over **Mansour et al.** (Mansour et al., Introduction of a lacZ reporter gene into the mouse int-2 locus by homologous recombination. *Proc Natl Acad Sci U S A.* 87(19):7688-92, 1990) in view of **Chernajovsky et al.** (Chernajovsky et al., Efficient constitutive production of human fibroblast interferon by hamster cells transformed with the IFN-beta 1 gene fused to an SV40 early promoter. *DNA* 3(4): 297-308, 1984), is ***withdrawn*** because Applicant's arguments filed on 05/12/2009 have been fully considered and found persuasive.

Applicant argues that the priority date of this application is March 20, 1989 (the filing date of FRANCE 89 03630), and the United States filing date is March 19, 1990 (the filing date

of PCT/FR90/00185), as no new matter is introduced. Applicant states that Mansour et al. was published after both of those dates; in October of 1990 (See pages 11-12 of Applicant's remarks file don 05/12/2009).

6. Previous rejection of claim 77 under 35 U.S.C. 103(a) as being unpatentable over **Mansour et al.** (Mansour et al., Introduction of a lacZ reporter gene into the mouse int-2 locus by homologous recombination. *Proc Natl Acad Sci U S A.* 87(19):7688-92, 1990) in view of **Lindenmaier et al.** (Lindenmaier et al., Isolation of a functional human interleukin 2 gene from a cosmid library by recombination in vivo. *Gene* 39(1): 33-9, 1985), is ***withdrawn*** because Applicant's arguments filed on 05/12/2009 have been fully considered and found persuasive.

Applicant argues that the priority date of this application is March 20, 1989 (the filing date of FRANCE 89 03630), and the United States filing date is March 19, 1990 (the filing date of PCT/FR90/00185), as no new matter is introduced. Applicant states that Mansour et al. was published after both of those dates, in October of 1990 (See pages 11-12 of Applicant's remarks filed on 05/12/2009).

7. Previous rejection of claims 71 and 74 under 35 U.S.C. 103(a) as being unpatentable over **Mansour et al.** (Mansour et al., Introduction of a lacZ reporter gene into the mouse int-2 locus by homologous recombination. *Proc Natl Acad Sci U S A.* 87(19):7688-92, 1990) in view of **Petkovich et al.** (Petkovich et al. A human retinoic acid receptor which belongs to the family of nuclear receptors. *Nature* 330(6147): 444-50, 1987) as applied to claim rejection of claims 71 and 73 above, and further in view of **George et al.** (George et al., Receptor density and cAMP

accumulation: analysis in CHO cells exhibiting stable expression of a cDNA that encodes the beta 2-adrenergic receptor. *Biochem Biophys Res Commun.* 150(2): 665-72, 1988) and **Emorine et al.** (Emorine et al., Molecular characterization of the human beta 3-adrenergic receptor. *Science* 245(4922): 1118-21, 1989), is ***withdrawn*** because Applicant's arguments filed on 05/12/2009 have been fully considered and found persuasive.

Applicant argues that the priority date of this application is March 20, 1989 (the filing date of FRANCE 89 03630), and the United States filing date is March 19, 1990 (the filing date of PCT/FR90/00185), as no new matter is introduced. Applicant states that Mansour et al. was published after both of those dates; in October of 1990 (See pages 11-12 of Applicant's remarks file don 05/12/2009).

8. Previous rejection of claims 71, 72 and 75 under 35 U.S.C. 103(a) as being unpatentable over **Mansour et al.** (Mansour et al., Introduction of a lacZ reporter gene into the mouse int-2 locus by homologous recombination. *Proc Natl Acad Sci U S A.* 87(19):7688-92, 1990) in view of **Petkovich et al.** (Petkovich et al. A human retinoic acid receptor which belongs to the family of nuclear receptors. *Nature* 330(6147): 444-50, 1987) as applied to claim rejection of claims 71 and 73 above, and further in view of **Sleckman et al.** (Sleckman et al., Expression and function of CD4 in a murine T-cell hybridoma. *Nature* 328(6128): 351-3, 1987), is ***withdrawn*** because Applicant's arguments filed on 05/12/2009 have been fully considered and found persuasive.

Applicant argues that the priority date of this application is March 20, 1989 (the filing date of FRANCE 89 03630), and the United States filing date is March 19, 1990 (the filing date of PCT/FR90/00185), as no new matter is introduced. Applicant states that Mansour et al. was

published after both of those dates; in October of 1990 (See pages 11-12 of Applicant's remarks file don 05/12/2009).

9. Claims 71 and 73 remain rejected under 35 U.S.C. 103(a) as being unpatentable over **Nandi et al.** (Nandi et al., Regulated expression of genes inserted at the human chromosomal beta-globin locus by homologous recombination. *Proc Natl Acad Sci U S A.* 85(11):3845-3849, 1988) in view of **Petkovich et al.** (Petkovich et al., A human retinoic acid receptor which belongs to the family of nuclear receptors. *Nature* 330(6147): 444-50, 1987). Applicant's arguments filed 05/12/2009 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 19-21 of the office action mailed on 11/12/2008.

For clarity and completeness of record, the rejection for the reasons of record advanced on pages 19-21 of the office action mailed on 11/12/2008, is reiterated below with revisions addressing claim amendments filed on 05/12/2009.

Nandi et al. teaches a plasmid carrying a modified human beta-globin gene and a foreign gene composed of the coding sequence of the bacterial neomycin-resistance gene linked to simian virus 40 transcription signals (SV*neo*) (See abstract, Nandi et al., 1988). Recombination resulted in stably transformed cells where the first flanking sequence recombined with the homologous first sequence of the genome and the second flanking sequence recombined with the homologous second endogenous sequence in the genome (See Fig. 1, Nandi et al., 1988, and Fig. 1 Smithies et al., 1985 which is cited in Nandi et al., 1988). The data indicates recombination was obtained in which the two genes were integrated at the beta-globin locus on human

chromosome 11 such that the first and second heterologous insertion DNA sequences are inserted into the genome between the first and second endogenous DNA sequences (See Fig. 1, Nandi et al., 1988). The genes inserted at the beta-globin locus were induced during differentiation, demonstrating proper insertion (See abstract, and Figure 1(a), see diagram and legend below, Nandi et al., 1988; the related **FIG. 1** of Smithies et al., *Nature*, 317: 230-234, 1985, cited in Nandi et al., 1988, is also included below for clarity of record).

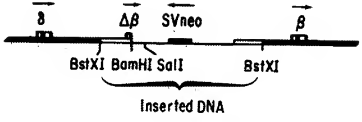

FIG. 1. (a) Structure of the modified human β-globin locus. The modification was produced by a homologous recombination between plasmid-derived human b-globin sequences (open bars) on pΔβ117 and resident human 13-globin sequences (solid bars) present in a Hu 11 MEL-human hybrid cell. The line indicates sequences mostly derived from pSV2neo, from which pΔβ117 was constructed. The position and direction of transcription of the globin (δ, Δβ, and β) and SV*neo* genes are indicated by the raised boxes and arrows.

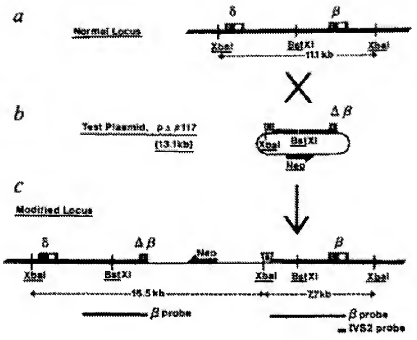

FIG. 1 of Smithies et al. (Nature, 317: 230-234, 1985, which applicant provided as Exhibit 1) cited by Nandi et al., 1988.

Nandi et al. 1988 does not teach (i) the first heterologous gene (i.e. a transgene to be knocked-in in a targeted locus in mammalian genome by homologous recombination) product is part or all of a receptor, as recited in claim 71, and (ii) wherein the receptor is a retinoic acid receptor, as recited in claim 73 of instant application.

However, at the time the claimed invention was made, the cDNA clone encoding a retinoic acid receptor was known in the art. For instance, Petkovich et al. disclose a cDNA clone encoding a retinoic acid receptor that binds retinoic acid with high affinity (See abstract, Petkovich et al., 1987).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the teachings Nandi et al. 1988 regarding the gene targeting construct comprising a modified β-globin gene for altering the endogenous genomic

copy of the β-globin gene locus, with the teachings of Petkovich et al. regarding a specific cDNA clone encoding retinoic acid receptor, by replacing Δβ sequences (i.e. the Δβ region been marked on its top with an arrow pointing right in Fig. 1 of Nandi et al., 1988) taught by Nandi et al. 1988 with the cDNA clone encoding a retinoic acid receptor taught by Petkovich et al., to arrive at the claimed DNA construct of claims 71 and 73.

One having ordinary skill in the art would have been motivated to substitute the Δβ sequences (the Δβ region been marked on its top with an arrow pointing right in Fig. 1 of Nandi et al., 1988the construct taught by Nandi et al. 1988 with the cDNA clone encoding retinoic acid receptor, which is heterologous with respect to the recipient gene -globin gene locus, taught by Petkovich et al. in order to drive the expression of a retinoic acid receptor gene bearing any intended modification and targeted it to a designed locus, rather than random integration which cause variations in expression of transgene expression in the genome of recipient cells, in the genome of recipient cells, thereby enabling the functional analysis of the retinoic acid receptor in a consistent genomic setting during differentiation and under different physiological conditions.

There would have been a reasonable expectation of success given (i) the construct taught by Nandi et al. 1988 can successfully alter gene of interest in a mammalian genome by homologous recombination and by selection of neomycin-resistance gene introduced by the construct, and (ii) the construct for cDNA clone encoding retinoic acid receptor was readily available by the teachings of Petkovich et al.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Applicant's arguments

Applicant states that the claimed vectors comprise both "a first heterologous insertion DNA sequence and a second heterologous insertion DNA sequence." Applicant states that in the claimed vectors "the first heterologous insertion DNA sequence encodes a first gene product that does not confer resistance to a selection agent involved in the selection of transformants" and "the second heterologous insertion DNA sequence encodes a second gene product that confers resistance to a selection agent involved in the selection of transformants." Applicant argues that, in contrast, the only heterologous DNA sequence in the vectors of **Smithies** (and thus Nandi), that encodes a gene product, is the one that encodes a gene product that confers resistance to a selection agent involved in the selection of transformants. Thus, the Nandi vector does not comprise a first heterologous insertion DNA sequence encoding a first gene product that does not confer resistance to a selection agent involved in the selection of transformants. Applicant states that, the Nandi vector does comprise a partial coding sequence of human beta-globin, and that sequence is homologous to endogenous sequences at the locus being targeted. Therefore, that sequence is part of a flanking DNA sequence homologous to an endogenous DNA sequence in the genome of a mammalian cell, and that sequence is not a "heterologous insertion DNA sequence" as recited in the amended claims. Therefore, Applicant states that, for that reason Nandi does not disclose every element of the pending claims (See page 13 of Applicant's remarks filed on 05/12/2009).

Response to Applicant's arguments

The Examiner acknowledges that Nandi et al. (1988) does not disclose every element of the pending claims because it is not a 102 rejection. However, as documented in the maintained 103 rejection, it would have been *prima facie* obvious to one having ordinary skill in the art at

the time of the invention to combine the teachings Nandi et al. 1988 regarding the gene targeting construct comprising a modified β-globin gene for altering the endogenous genomic copy of the β-globin gene locus, with the teachings of Petkovich et al. regarding a specific cDNA clone encoding retinoic acid receptor, by replacing Δβ sequences (i.e. the Δβ region been marked on its top with an arrow pointing right in Fig. 1 of Nandi et al., 1988) taught by Nandi et al. 1988 with the cDNA clone encoding a retinoic acid receptor taught by Petkovich et al., to arrive at the claimed DNA construct of claims 71 and 73. One having ordinary skill in the art would have been motivated to substitute the Δβ sequences (the Δβ region been marked on its top with an arrow pointing right in Fig. 1 of Nandi et al., 1988§the construct taught by Nandi et al. 1988 with the cDNA clone encoding retinoic acid receptor, which is heterologous with respect to the recipient gene β-globin gene locus, taught by Petkovich et al. in order to drive the expression of a retinoic acid receptor gene bearing any intended modification and targeted it to a designed locus, rather than random integration which cause variations in expression of transgene expression in the genome of recipient cells, thereby enabling the functional analysis of the retinoic acid receptor in a consistent genomic setting during differentiation and under different physiological conditions.

It is worth noting that the limitation "the first heterologous insertion DNA sequence encodes a first gene product that does not confer resistance to a selection agent involved in the selection of transformants" reads on any transcription product (RNA) and translation product (protein), either before or after recombination event occurs. In this regard, the truncated transcription product (RNA) and truncated translation product (protein) expressed by the Δβ sequences after recombination event is certainly encompassed by the limitation. Also the claims

do not require the gene product to be "complete" or "functional." Since there is no requirement for the inserted DNA to be genomic DNA, and thus can be a cDNA, the term "gene product" is anything encoded by the "gene". Furthermore, replacing Δβ sequences taught by Nandi et al. 1988 with the complete and functional cDNA clone encoding a retinoic acid receptor taught by Petkovich et al. would maintain the flanking sequences (open bars marked in Fig. 1 of Nandi et al., 1988) required for homologous recombination to occur.

10. Claim 76 remains rejected under 35 U.S.C. 103(a) as being unpatentable over **Nandi et al.** (Nandi et al., Regulated expression of genes inserted at the human chromosomal beta-globin locus by homologous recombination. *Proc Natl Acad Sci U S A.* 85(11):3845-3849, 1988) in view of **Chernajovsky et al.** (Chernajovsky et al., Efficient constitutive production of human fibroblast interferon by hamster cells transformed with the IFN-beta 1 gene fused to an SV40 early promoter. *DNA* 3(4): 297-308, 1984). Applicant's arguments filed 05/12/2009 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 21-22 of the office action mailed on 11/12/2008.

For clarity and completeness of record, the rejection for the reasons of record advanced on pages 21-22 of the office action mailed on 11/12/2008, is reiterated below with revisions addressing claim amendments filed on 05/12/2009.

The teachings of Nandi et al., 1988 have been discussed in the preceding rejection of claims 71 and 73 under 35 U.S.C. 103(a) as being unpatentable over Nandi et al. (1988) in view of Petkovich et al. (1987).

Nandi et al. (1988) does not teach (i) the first heterologous gene (i.e. a transgene to be knocked-in in a targeted locus in mammalian genome by homologous recombination) product is part or all of an interferon, as recited in claim 76 of instant application.

However, at the time the claimed invention was made, the cDNA clone encoding an interferon was known in the art. For instance, Chernajovsky et al. teach the construction of the plasmid pSVEIF, which harbors the interferon β1 (INF-β1) gene (See Figure 1, Chernajovsky et al., 1984).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the teachings Nandi et al. 1988 regarding the gene targeting construct comprising a modified β-globin gene for altering the endogenous genomic copy of the β-globin gene locus, with the teachings of Chernajovsky et al. regarding a specific cDNA clone encoding interferon β1, by replacing Δβ sequences (i.e. the Δβ region been marked on its top with an arrow pointing right in Fig. 1 of Nandi et al., 1988) taught by Nandi et al. 1988 with the cDNA clone encoding interferon β1 taught by Chernajovsky et al., to arrive at the claimed DNA construct of claim 76.

One having ordinary skill in the art would have been motivated to substitute the modified β-globin gene construct taught by Nandi et al. 1988 with the cDNA clone encoding interferon β1 taught by Chernajovsky et al. in order to drive the expression of interferon β1 gene bearing any intended modification and targeted it to a designed locus, rather than random integration which cause variations in expression of transgene expression in the genome of recipient cells, thereby enabling the functional analysis of the interferon β1 in a consistent genomic setting during differentiation and under different physiological conditions.

There would have been a reasonable expectation of success given (i) the construct taught by Nandi et al. 1988 can successfully alter gene of interest in a mammalian genome by homologous recombination and by selection of neomycin-resistance gene introduced by the construct, and (ii) the construct for cDNA clone encoding interferon β1 was readily available by the teachings of Chernajovsky et al.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Applicant's arguments and Examiner's ***response to Applicant's arguments*** are the same as documented in the maintained rejection of claims 71 and 73 rejected under 35 U.S.C. 103(a) as being unpatentable over Nandi et al. in view of Petkovich et al.

11. Claim 77 remains rejected under 35 U.S.C. 103(a) as being unpatentable over **Nandi et al.** (Nandi et al., Regulated expression of genes inserted at the human chromosomal beta-globin locus by homologous recombination. *Proc Natl Acad Sci U S A.* 85(11):3845-3849, 1988) in view of **Lindenmaier et al.** (Lindenmaier et al., Isolation of a functional human interleukin 2 gene from a cosmid library by recombination in vivo. *Gene* 39(1): 33-9, 1985). Applicant's arguments filed 05/12/2009 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 23-24 of the office action mailed on 11/12/2008.

For clarity and completeness of record, the rejection for the reasons of record advanced on pages 23-24 of the office action mailed on 11/12/2008, is reiterated below with revisions addressing claim amendments filed on 05/12/2009.

The teachings of Nandi et al., 1988 have been discussed in the preceding rejection of claims 71 and 73 under 35 U.S.C. 103(a) as being unpatentable over Nandi et al. (1988) in view of Petkovich et al. (1987).

Nandi et al. (1988) does not teach (i) the first heterologous gene (i.e. a transgene to be knocked-in in a targeted locus in mammalian genome by homologous recombination) product is part or all of an interleukin, as recited in claim 77 of instant application.

However, at the time the claimed invention was made, the cDNA clone encoding an interleukin was known in the art. For instance, Lindenmaier et al. teach the construction of the plasmid pAN26-IL2, which harbors the interleukin 2 gene (IL2) (See Figure 1, Lindenmaier et al., 1985).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the teachings Nandi et al. 1988 regarding the gene targeting construct comprising a modified β-globin gene for altering the endogenous genomic copy of the β-globin gene locus, with the teachings of Lindenmaier et al. regarding a specific cDNA clone encoding interleukin 2 gene, by replacing Δβ sequences (i.e. the Δβ region been marked on its top with an arrow pointing right in Fig. 1 of Nandi et al., 1988) taught by Nandi et al. 1988 with the cDNA clone encoding interleukin 2 taught by Lindenmaier et al., to arrive at the claimed DNA construct of claim 77.

One having ordinary skill in the art would have been motivated to substitute the modified β-globin gene construct taught by Nandi et al. 1988 with the cDNA clone encoding in interleukin 2 gene taught by Lindenmaier et al. in order to drive the expression of interleukin 2 gene bearing any intended modification and targeted it to a designed locus, rather than random integration

which cause variations in expression of transgene expression in the genome of recipient cells, thereby enabling the functional analysis of the interleukin 2 in a consistent genomic setting during differentiation and under different physiological conditions.

There would have been a reasonable expectation of success given (i) the construct taught by Nandi et al. 1988 can successfully alter gene of interest in a mammalian genome by homologous recombination and by selection of neomycin-resistance gene introduced by the construct, and (ii) the construct for cDNA clone encoding interleukin 2 gene was readily available by the teachings of Lindenmaier et al.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Applicant's arguments and Examiner's ***response to Applicant's arguments*** are the same as documented in the maintained rejection of claims 71 and 73 rejected under 35 U.S.C. 103(a) as being unpatentable over Nandi et al. in view of Petkovich et al.

12. Claims 71 and 74 remain rejected under 35 U.S.C. 103(a) as being unpatentable over **Nandi et al.** (Nandi et al., Regulated expression of genes inserted at the human chromosomal beta-globin locus by homologous recombination. *Proc Natl Acad Sci U S A.* 85(11):3845-3849, 1988) in view of **Petkovich et al.** (Petkovich et al. A human retinoic acid receptor which belongs to the family of nuclear receptors. *Nature* 330(6147): 444-50, 1987) as applied to claim rejection of claims 71 and 73 above, and further in view of **George et al.** (George et al., Receptor density and cAMP accumulation: analysis in CHO cells exhibiting stable expression of a cDNA that encodes the beta 2-adrenergic receptor. *Biochem Biophys Res Commun.* 150(2): 665-72, 1988)

and **Emorine et al.** (Emorine et al., Molecular characterization of the human beta 3-adrenergic receptor. *Science* 245(4922): 1118-21, 1989). Applicant's arguments filed 05/12/2009 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 24-26 of the office action mailed on 11/12/2008.

For clarity and completeness of record, the rejection for the reasons of record advanced on pages 23-24 of the office action mailed on 11/12/2008, is reiterated below with revisions addressing claim amendments filed on 05/12/2009.

The teachings of Nandi et al. 1988 and Petkovich et al. 1987 have been discussed in the preceding rejection of claims 71 and 73 under 35 U.S.C. 103(a) as being unpatentable over Nandi et al. 1988 and Petkovich et al. 1987.

Nandi et al. 1988 and Petkovich et al. 1987 do not teach the receptor is a 3- adrenergic receptor, as recited in claim 74 of instant application.

However, at the time the claimed invention was made, the cDNA clone encoding a 3-β adrenergic receptor was known in the art. For instance, George et al. disclose a plasmid pUC13B2AR containing a beta 2-adrenergic receptor (See Material and Methods, page 666, George et al., 1988) and Emorine et al. teach that human beta 3-adrenergic receptor shares 45.5% identical amino acid sequences of human beta 2-adrenergic receptor.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the teachings of Nandi et al. 1988 and Petkovich et al. 1987 regarding the gene targeting construct comprising a retinoic acid receptor inserted in the endogenous genomic copy of the β-globin gene, with the teachings of George et al. and Emorine

et al. regarding a specific cDNA clone encoding a beta 3-adrenergic receptor, by replacing Δβ sequences (i.e. the Δβ region been marked on its top with an arrow pointing right in Fig. 1 of Nandi et al., 1988) taught by Nandi et al. 1988 with the cDNA clone encoding a beta 3-adrenergic receptor taught by George et al. and Emorine et al., to arrive at the claimed DNA construct of claim 74.

One having ordinary skill in the art would have been motivated to incorporate the teachings of Nandi et al., 1988 and Petkovich et al. 1987 with the cDNA clone encoding an beta 3-adrenergic receptor taught by George et al. and Emorine et al. in order to drive the expression of beta 3-adrenergic receptor gene bearing any intended modification and targeted it to a designed locus, rather than random integration which cause variations in expression of transgene expression in the genome of recipient cells, thereby enabling the functional analysis of the beta 3-adrenergic receptor a consistent genomic setting during differentiation and under different physiological conditions.

There would have been a reasonable expectation of success given (i) the construct taught by Nandi et al. 1988 and Petkovich et al. 1987 can successfully alter gene of interest in a mammalian genome, including a retinoic acid receptor, by homologous recombination and by selection of neomycin-resistance gene introduced by the construct, and (ii) the construct for cDNA clone encoding a beta 3-adrenergic receptor was readily available by the combined teachings of George et al. and Emorine et al.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Applicant's arguments and Examiner's ***response to Applicant's arguments*** are the same as documented in the maintained rejection of claims 71 and 73 rejected under 35 U.S.C. 103(a) as being unpatentable over Nandi et al. in view of Petkovich et al.

13. Claims 71, 72 and 75 remain rejected under 35 U.S.C. 103(a) as being unpatentable over **Nandi et al.** (Nandi et al., Regulated expression of genes inserted at the human chromosomal beta-globin locus by homologous recombination. *Proc Natl Acad Sci U S A.* 85(11):3845-3849, 1988) in view of **Petkovich et al.** (Petkovich et al. A human retinoic acid receptor which belongs to the family of nuclear receptors. *Nature* 330(6147): 444-50, 1987) as applied to claim rejection of claims 71 and 73 above, and further in view of **Sleckman et al.** (Sleckman et al., Expression and function of CD4 in a murine T-cell hybridoma. *Nature* 328(6128): 351-3, 1987). Applicant's arguments filed 05/12/2009 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 26-28 of the office action mailed on 11/12/2008.

For clarity and completeness of record, the rejection for the reasons of record advanced on pages 26-28 of the office action mailed on 11/12/2008, is reiterated below with revisions addressing claim amendments filed on 05/12/2009.

The teachings of Nandi et al., 1988 and Petkovich et al. 1987 have been discussed in the preceding rejection of claims 71 and 73 under 35 U.S.C. 103(a) as being unpatentable over Nandi et al., 1988 and Petkovich et al. 1987.

Nandi et al., 1988 and Petkovich et al. 1987 do not teach the receptor is a receptor for infectious agent recited in claim 72, and an HIV receptor recited in claim 75 of instant application.

However, at the time the claimed invention was made, the cDNA clone encoding a HIV receptor CD4 was known in the art. For instance, Sleckman et al. teach the retroviral vector construction MNST4, which harbors the CD4 gene (the receptor of infectious HIV) (See Figure 1, Sleckman et al., 1987). HIV is an infectious agent (as recited in claim 72) and the CD4 is a cellular receptor of HIV. Through interaction between which HIV envelope protein and CD4 receptor present on cell surface (an HIV receptor as recited in claim 75), the HIV can infect the cell.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to incorporate the teachings Nandi et al., 1988 and Petkovich et al. 1987, regarding the gene targeting construct comprising a retinoic acid receptor inserted in the endogenous genomic copy of the β-globin gene, with the teachings of Sleckman et al. regarding a specific cDNA clone encoding HIV receptor, by replacing Δβ sequences (i.e. the Δβ region been marked on its top with an arrow pointing right in Fig. 1 of Nandi et al., 1988) taught by Nandi et al. 1988 with the cDNA clone encoding a HIV receptor taught by Sleckman et al., to arrive at the claimed construct of claims 72 and 75.

One having ordinary skill in the art would have been motivated to incorporate the teachings of Nandi et al., 1988 and Petkovich et al. 1987 with the teachings of Sleckman et al. in order to drive the expression of a HIV receptor gene bearing any intended modification and targeted it to a designed locus, rather than random integration which cause variations in

expression of transgene expression in the genome of recipient cells, thereby enabling the functional analysis of the HIV receptor in a consistent genomic setting during pathogenesis of AIDS and under different physiological conditions.

There would have been a reasonable expectation of success given (i) the construct taught by Nandi et al., 1988 and Petkovich et al. 1987 can successfully alter gene of interest in a mammalian genome, including a retinoic acid receptor, by homologous recombination and by selection of neomycin-resistance gene introduced by the construct, and (ii) the construct for cDNA clone encoding an HIV receptor CD4 was readily available by the teachings of Sleckman et al.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Applicant's arguments and Examiner's ***response to Applicant's arguments*** are the same as documented in the maintained rejection of claims 71 and 73 rejected under 35 U.S.C. 103(a) as being unpatentable over Nandi et al. in view of Petkovich et al.

Conclusion

14. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

15. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, Jr. can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Deborah Crouch/
Primary Examiner, Art Unit 1632